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X = Y - ZH Systems as Potential 1,3-Dipoles. Part 40.[1]

Chiral Azomethine Ylides from Homochiral Cyclic α-Amino Esters. Unusual Regiospecific Deprotonation of Iminium Ions.

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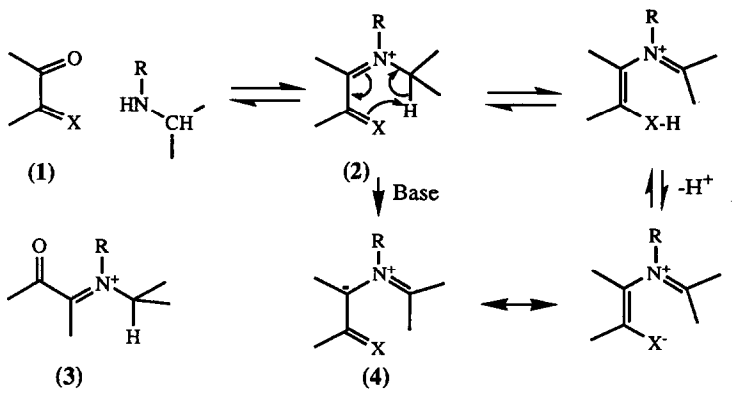
Abstract. *$A^{1,3}$-Strain and charge accelerated 1,5-H shifts are important factors in the stereospecific formation of iminium ions from cyclic secondary α-amino esters and bifunctional carbonyl compounds and their regiospecific or regioselective conversion to homochiral azomethine ylides. The endo-exo selectivity in the cycloadditions of these azomethine ylides is sensitive to the bifunctional carbonyl compound employed.*

We have previously reported details of our iminium ion route to azomethine ylides (Scheme 1)[2] whereby a bifunctional compound (1) reacts with an amine to produce an iminium species (2) and subsequently an azomethine ylide either via a 1,5-H shift in (2) (Scheme 1) or by intervention of an external base to deprotonate (2).

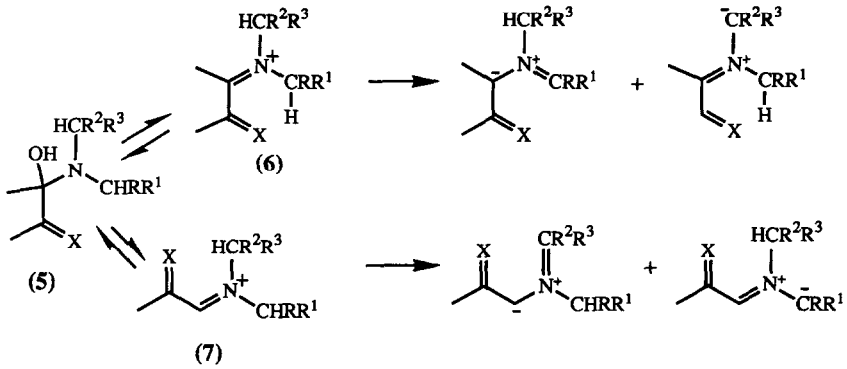


Scheme 1

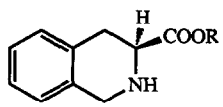
Our previous studies[2] were concerned with substrates in which any α-protons in the group R in iminium ion (2) were kinetically inert. Thus the alternative iminium ion (3) if formed did not exhibit a 1,5-H shift involving R (R=CH<) and no azomethine ylides arising from deprotonation at R in (2) or (3) were observed. Our conclusions in the previous study were that the substrates kinetically favoured iminium ion (2) and, on the data available, external base deprotonation (2) → (4) occurred in certain cases although there was clear evidence

of a stereoelectronic interaction between X and CH in (2).[2] It was therefore of interest to study secondary amine substrates in which both amine substituents, upon iminium ion formation would possess kinetically labile protons (Scheme 2). Thus carbinolamine (5) could give rise to iminium ions (6) and (7) and these in turn are each potential precursors of two azomethine ylides depending on the regioselectivity of deprotonation or the operation of a 1,5-H shift (Scheme 2).

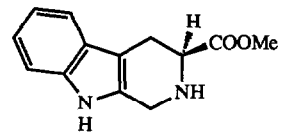
Three chiral cyclic secondary α-amino esters (8) - (10) were selected to evaluate Scheme 2 together with four bifunctional carbonyl compounds (11a,b) - (13).



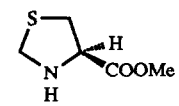
Scheme 2



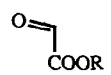
(8) a. R= Me
b. R= CH_2Ph

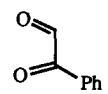


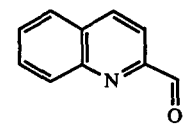
(9)



(10)





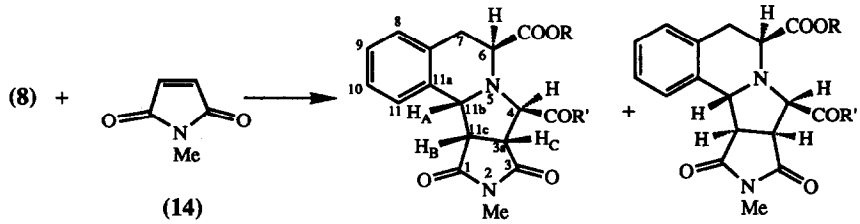


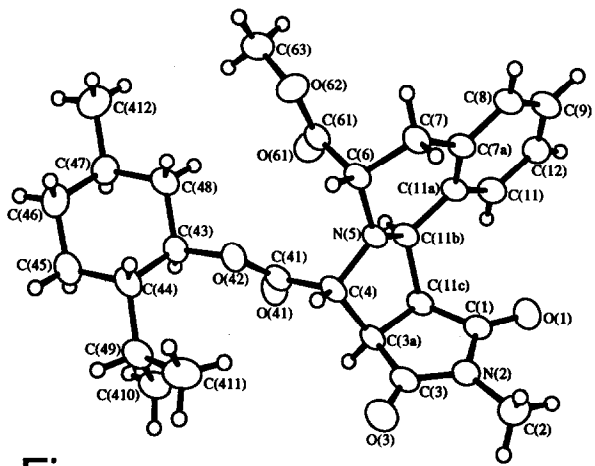
(11) a. R=(+)-Menthyl
b. R= Me

(12)

(13)

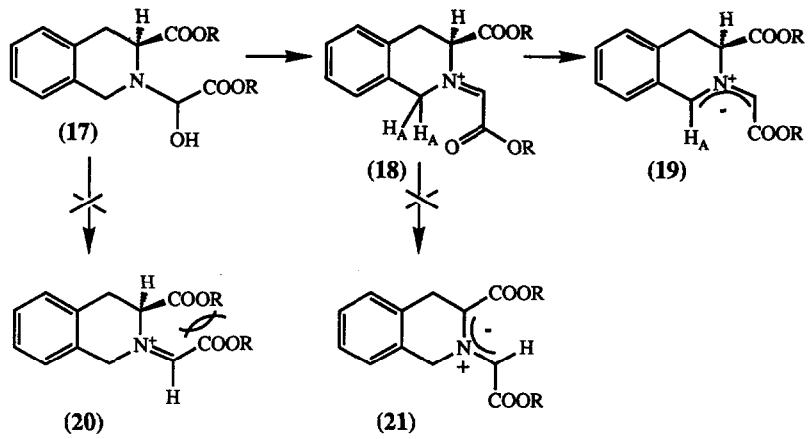
Reaction (DMF, 110°C, 18h) of (8a) with (11a) and N-methylmaleimide (14) afforded a 5:1 mixture of homochiral cycloadducts (15a) ($[\alpha]_D$ 140.2°) and (16a) ($[\alpha]_D$ 118.8°) in 73% combined yield. Both cycloadducts arise from azomethine ylide (19) showing that carbinolamine (17) generates iminium ion (18) and not (20) and that (18) undergoes regiospecific conversion to (19) and not (21) (Scheme 3). The stereochemistry of (15a) and (16a) were established by n.O.e. studies and confirmed unequivocally in the case of (15a) by an X-rays crystal structure (figure).



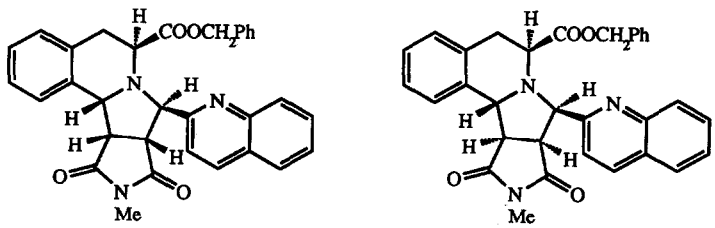


Figure

Thus the absolute stereochemistry of the central fused ring system in (15a) is 3aR, 4R, 6S, 11bR, 11cS. Whilst (16a) is the 3aS, 4R, 6S, 11bR, 11cR isomer. Stereospecific conversion of carbinolamine (17) into iminium ion (18) reflects the higher energy transition state for (17) → (20) consequent on the developing $A^{1,3}$-strain[3] between the two ester substituents (Scheme 3). We have noted such effects before in stereospecific azomethine ylide formation.[4] Perhaps more remarkable is the lack of any deprotonation of (18) to (21) which again attests to a stereoelectronic interaction between the carbonyl group of the methyl ester and the benzylic CH_2^ group in (18). Extensive experience with azomethine ylides has shown that maleimide dipolarophiles trap the dipole(s) formed under kinetic control[5] which rules out any process involving dipole equilibration and kinetic selection of (19) in competition with (21). Carbinolamine → iminium ion is considered to be the rate determining step in all the cycloaddition cascades discussed in this paper[4]. When the reaction was repeated with (8b) and methyl glyoxalate under milder conditions (MeCN, 80°C, 16h) (85% conversion to products) the product comprised a 3:1 mixture of (15b) and (16b) in 71% yield. Once again the stereochemistry of the cycloadducts was assigned based on n.O.e. data (see experimental section) and again both (15b) and (16b) were homochiral. Although the reactions in DMF go to completion, small amounts of other products (diasteromers?) are also formed whilst in acetonitrile these by-products are not observed.

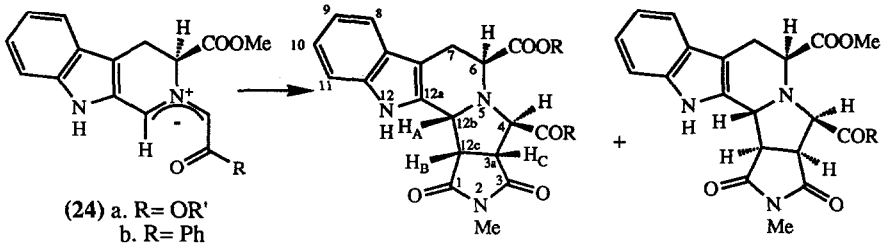


Scheme 3



Reaction (MeCN, 80°, 6h) of (8b) with (12) and (14) afforded a single homochiral cycloadduct (15c) ($[\alpha]_D$ 150.5°) in 78% yield, whilst use of (13) as the bifunctional carbonyl component with (8b) resulted (MeCN, 80°C, 20h) (70% conversion) in the lowest endo-exo selectivity, furnishing a 3:2 mixture (64%) of homochiral (22) and (23).

An analogous trend was observed when the tetrahydro-β-carboline (9) was reacted with (11a,b). Thus (9), (11a) and (14) react (DMF, 120°C) via stereospecific formation of (24) to give a 3.5:1 mixture of two isomeric cycloadducts (25a) and (presumably) (26a). The major isomer (25a) ($[\alpha]_D$ 104.2°) was isolated in 51% yield by chromatography but attempts to isolate the minor isomer were unsuccessful. However, an analogous reaction (MeCN, 80°C, 15h) using methyl glyoxalate proceeded to 76% conversion and afforded a 3:1 mixture (68%) of homochiral (25b) and (26b), which was separable by flash chromatography. Stereochemical assignments are again based on n.O.e. data. Thus for (25b) irradiation of the 12b-H caused enhancement of 12c-H (15.1%) and irradiation of 3a-H caused enhancement of 12c-H (13.2%) and 4-H (4.4%), whilst for (26b) irradiation of 12b-H caused enhancement of 12c-H (4.6%) and irradiation of 4-H caused enhancement of 3a-H (12.4%).



(24) a. R= OR'
b. R= Ph

(25) a. R=(+)-OMenthyl
b. R= OMe
c. R= Ph

(26)

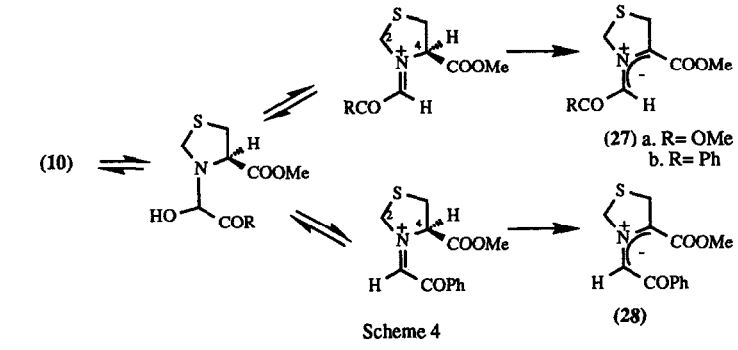
Reaction (MeCN, 80°C, 20h) of the tetrahydro-β-carboline (9) with phenylglyoxal (12) and N-methylmaleimide (14) afforded a single homochiral cycloadduct (25c) in 73% yield (67% conversion).

The importance of the fused aromatic ring in (8) and (9) in controlling the regioselectivity of deprotonation of the derived iminium ions is illustrated by the reaction (DMF, 120°C, 12h) of the thiazolidine (10), methyl glyoxalate (11a) and N-methylmaleimide (14). Work up in the usual way followed by flash chromatography afforded four cycloadducts (29a-32a) (total 68%) together with a mixture of two diasteromers of dimethyl thiazolidine-2,5-dicarboxylate (33) (25%). The stereochemistry of (29a-32a) was assigned on the basis of n.O.e. data (see experimental). Thus in this case the intermediate carbinolamine (Scheme 4) furnishes a single iminium ion which, in turn, gives rise to the azomethine ylide (27a) via regiospecific deprotonation at C(4). Minor cycloadducts (31a) and (32a) arise from condensation of small amounts of formaldehyde liberated in the formation of (33). There is a ca. 2:1 preference for an endo-transition state over an exo-transition state in the formation of (29a) (37%) and (30a) (18.4%). The minor cycloadducts (31a) and (32a) were obtained in approximately 10% combined yield. No cycloadducts arising from azomethine ylides derived from (33) were observed.

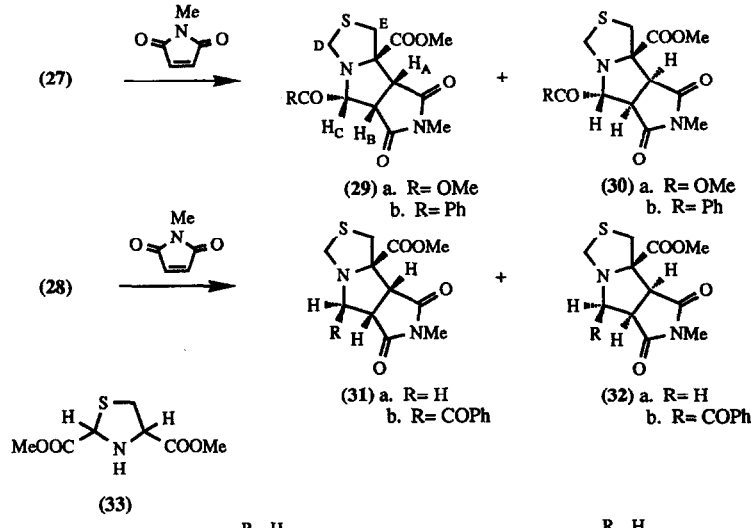
An analogous reaction (DMF, 120°C, 16h) between (10), phenylglyoxal (12) and NMM afforded a 2.7:1:1 mixture (73%) of (29b), (30b), and (31b). No (32b) was detected nor was any aldehyde exchange product analogous to (33) isolated. Thus in this case a 3.7:1 mixture of azomethine ylides (27b) and (28) are formed under kinetic control and there is a 2.7:1 preference for the endo- over the exo- transition state in the cycloaddition of (27b) and NMM.

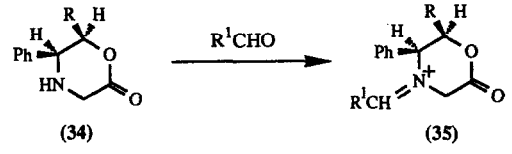
The importance of the rigidity imparted by aryl ring fusion in iminium ion (18) and the corresponding β-carboline iminium ion is illustrated by iminium ions (35) derived from oxazinone (34). These deprotonate exclusive at the methylene group α to the carbonyl moiety. Cycloaddition reactions of these species were pioneered by Williams[5] and extensively developed by Harwood.[6] The interdependence of aryl ring fusion and a bifunctional carbonyl compound is further demonstrated by the reaction (toluene, 110°C, 18h) of homochiral (8a), 2-methoxybenzaldehyde (36) and (14) which affords a 1:1.2 mixture of racemic cycloadducts (38) and (39). In this case the intermediate ion (37) deprotonates exclusively α to the ester group. Hence the ortho-methoxy group in (37) is not an effective substitute for C=O or C=N.

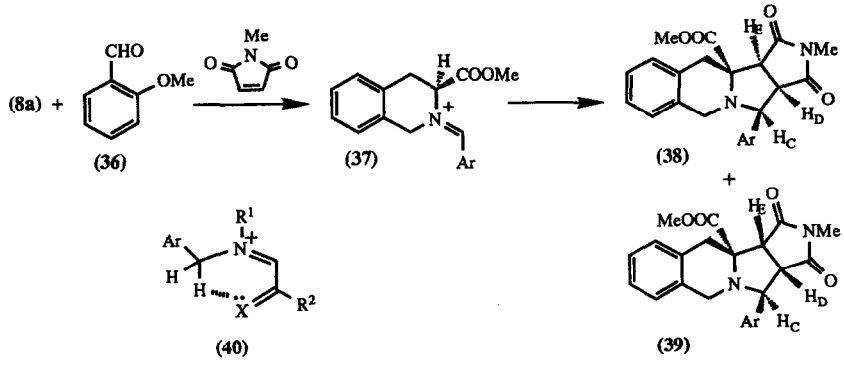
In conclusion, the regiospecific formation of iminium ions from carbinolamines derived from cyclic secondary α-amino esters is controlled by $A^{1,3}$-strain[4] and stereoelectronic effects between acidic benzylic protons and lone pair atoms (40)[2] in the transition states whilst the regioselectivity of the "deprotonation" of these iminium ions reflects competition between deprotonation by an external base and a 1,5-H shift accelerated by the positive charge on the system.[7]


(10)
HO
COR
RCO
COOMe
(27) a. R= OMe
b. R= Ph
COPh
(28)

Scheme 4


(27)
(28)
Me
(29) a. R= OMe
b. R= Ph
(30) a. R= OMe
b. R= Ph
(31) a. R= H
b. R= COPh
(32) a. R= H
b. R= COPh
(33)


R¹CHO
(34)
(35)


(8a) +
(36)
(37)
(38)
(39)
(40)

Experimental. Experimental details were as previously noted.[8] Petroleum ether refers to the fraction with b.p. 40-60°C. Flash chromatography employed Silica Gel 60 (Merck). The chiral cyclic α-amino esters (8a),[9] (8b),[9] (9)[10] and (10)[11] were prepared by literature methods.

General Procedure. A solution of the α-amino ester (1mmol), bifunctional carbonyl compound (1mmol) and N-methylmaleimide (1mmol) in dry DMF or acetonitrile (15-20ml) was heated at 80-120°C for the time noted. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography. Optical rotations were measured at 25°C.

(3aR, 4R, 6S, 11bR, 11cS)-2,3,3aβ, 4α, 6α, 7, 11bβ, 11cβ-Octahydro-4-[1′R, 2′S, 5′R)-2′-isopropyl-5′-methylcyclohexyloxycarbonyl]-6-methoxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione (15a) and (3aS, 4R, 6S, 11bR, 11cR)-2,3,3aα,4α,6α,7,11bβ,11cα-octahydro-4-[(1′R, 2′S, 5′R)-2′-isopropyl-5′-methylcyclohexyloxycarbonyl]-6-methoxycarbonyl-2-methyl-1-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3 dione (16a). Prepared from methyl (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.36g) in DMF(20ml) at 110°C for 15h. The pmr spectrum of the reaction mixture showed the presence of a 5:1 mixture of two isomeric cycloadducts. Flash chromatography eluting with 7:3v/v ether-petroleum ether afforded (15a) and (16a) (0.68g, 73%).

15a Crystallised from ether-petroleum ether as colourless prisms, m.p. 147-149°C, $[\alpha]_D$+140.2° (c.0.082,$CHCl_3$); (Found: C,67.45; H,7.35; N, 5.55. $C_{28}H_{36}N_2O_6$ requires C, 67.7; H, 7.2; N, 5.6%); δ 7.38 (d, 1H, J 7.5Hz, ArH), 7.27 and 7.25 (2xt, 2x1H, ArH), 7.02 (d, 1H, J 7.5Hz, ArH), 5.29 (d, 1H, J 7.65Hz, 11b-H), 4.71 (dt, 1H, J 4.3 and 6.5Hz, menthyl-H), 4.21 (s, 1H, 4-H), 4.00 (dd, 1H, J 6.5 and 2.3Hz, 6-H), 3.72 (dd, 1H, J 7.7 and 7.7Hz, 11c-H), 3.63 (d, 1H, J 7.7Hz, 3a-H), 3.58 (s, 3H, OMe), 3.15 (dd, 1H, J 6.5 and 15.9Hz,7-H), 2.89 (dd, 1H, J 15.7 and 1.75Hz, 7-H), 2.83 (s, 3H, NMe), 2.01 (d, 1H, J 9.5Hz, menthyl-H), 1.89 (m, 1H, menthyl-H), 1.67 (m, 3H, menthyl-H), 0.93 and 0.89 (2xd, 2x3H, $CH\underline{Me}_2$), and 0.78 (3H, J 6.95 Hz, Me); m/z(%) 496(M^+,5), 358(32), 357(100), 314(25), 299(32), 255(8), 168(39) and 130(17).

16a Crystallised from ether-petroleum ether as colourless needles, m.p. 196-198°C, $[\alpha]_D$ + 118.7° (c.0.12, $CHCl_3$); (Found: C, 67.3; H, 6.95; N, 5.25%); δ 7.42 (d, 1H, J 7.6 Hz, ArH), 7.29-7.22 (m, 2H, ArH), 7.17 (d, 1H, J 7.8Hz, ArH), 4.88 (dt, 1H, J 4.35 and 6.6Hz, menthyl-H), 4.48 (d, 1H, J 6.6Hz, 4-H), 4.25 (d, 1H, J 5.95Hz, 6-H), 4.10 (d, 1H, J 7.65, 11b-H), 3.61 (t, 1H, 3a-H), 3.60 (s, 3H, OMe), 3.58 (t, 1H, 11c-H), 3.34 (dd, 1H, J 6.05 and 16.95Hz, 7-H), 3.05 (d, 1H, J 16.6Hz, 7-H), 2.85 (s, 3H, NMe), 2.30 (d, 1H, J 7.5Hz, menthyl-H), 1.83-1.19 (m, 5H, menthyl-H), 1.15-1.03 (m, 3H, menthyl-H), 0.96 and 0.89 (2xd, 2x3H, $CH\underline{Me}_2$), and 0.76 (d, 3H, J 6.9Hz, Me); m/z(%) 496 (M^+,3), 357(25), 313(100), 299(28), 298(4), 254(6), 183(6), 143(7), 139(9), 131(4), 111(8) and 59(5).

Benzyl esters (15b) and (16b). Prepared in boiling acetonitrile over 16h. The pmr spectrum indicated 85% conversion to a 3:1 mixture of (15b) and (16b). Flash chromatography eluting with 8:2 v/v ether-petroleum ether afforded the two isomers.

15b Crystallised from ether-hexane as fine colourless prisms, m.p. 159°C, $[\alpha]_D$ + 228°(c.0.4, CH_2Cl_2); (Found: C, 67.1; H, 5.4; N, 6.15. $C_{25}H_{25}N_2O_6$ requires C, 66.8; H, 5.55; N, 6.25%); m/z(%) 449(M^+,1), 389(25), 357(100), 313(80), 202(25), 168(37), 130(41), 91(79), and 69(29); δ 7.4-7.1(m, 9H, ArH), 5.22(d, 1H J 7Hz, 11b-H), 5.0(q, 2H, J 13.6, 25.8 and 12.6Hz, $PhCH_2$) 4.2(s, 1H, 4-H), 4.08(m, 1H, 6-H), 3.73(t, 1H, J 7.5 and 7.5 Hz, 11c-H), 3.67(d, 1H, J 7.7, 3a-H), 3.52(s, 3H, OMe), 3.19(dd, 1H, J 6.6 and 6.8Hz, $ArCH_2$), 2.95(d, 1H, J 7.3Hz, $ArCH_2$) and 2.83(s, 3H, NMe); ^1H NOEDS(%): irradiation of 11b-H caused enhancement of the signal for 11c-H (15.76). Irradiation of 3a-H caused enhancement the signal for 11c-H (16.2) and 4-H (3.8).

16b Crystallised from ether as fine colourless needles, m.p. 207°C, $[\alpha]_D$ + 116.4° (c.0.33, CH_2Cl_2); (Found: C, 66.75; H, 5.45; N, 6.05%); m/z(%) 449(M^+,3), 389(15), 357(100), 313(87), 168(30) and 91(58); δ 7.41-7.07(m, 9H, ArH), 5.03(q, 2H, J 12.5, 10.7 and 12.7Hz, $PhCH_2$), 4.51(d, 1H, J 7.1Hz, 11b-H), 4.38(m, 1H, 6-H), 4.27(d, 1H, J 7.7Hz, 4-H), 3.83(s, 3H, OMe), 3.61(t, 1H, J 7.5 and 7.3Hz, 11c-H), 3.55(t, 1H, J 7.7Hz, 3a-H), 3.33(dd, 1H, J 6.8 and 6.4Hz, 7-H), 3.13(d, 1H, J 16.2Hz, 7-H), and 2.84(s, 3H, NMe); ^{1}H NOEDS(%): irradiation of 11b-H caused enhancement of the signal for 11c-H (5.1). Irradiation of 4-H proton caused enhancement of 3a-H (13.1).

(3aR, 4R, 6S, 11bR, 11cS)-2,3,3aβ, 4α, 6α, 7, 11bβ, 11cβ-Octahydro-4-benzoyl-6-benzyloxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15c). Prepared from benzyl (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate in boiling acetonitrile over 6h. Work up followed by flash chromatography eluting with 7:3 v/v petroleum ether-ethyl acetate afforded the product (78%) which crystallised from dichloromethane-petroleum ether as pale yellow needles, m.p. 163°C; $[\alpha]_D$ + 150.5° (c.0.88, MeOH); (Found: C, 72.8; H, 5.35; N, 5.45. $C_{30}H_{26}N_2O_5$ requires C, 72,85; H, 5.25; N, 5.65%); m/z(%) 494(M^+,10), 389(100), 266(54), 209(34), 177(99), 91(83) and 72(22); δ 8.1(d, 2H, J 7.2Hz, ArH), 7.6-6.9(m, 12H, ArH), 5.27(s, 1H, 4-H), 5.15(d, 1H, J 8.5Hz, 11b-H), 4.71(s, 2H, $PhCH_2$), 3.95(m, 1H, 6H), 2.62(m, 2H, 11c-H, 3a-H), 3.07-2.94(m, 2H, $ArCH_2$), and 2.87(s, 3H, NMe); ^{1}H NOEDS(%): irradiation of 11b-H proton caused enhancement of the signal for 11c-H (12.1). Irradiation of 4-H caused enhancement the signal for 3a-H (4.2).

(3aR, 4R, 6S, 11bR, 11cS)-2,3,3aβ, 4α, 6α, 7, 11bβ, 11cβ-Octahydro-4-(2′-quinolinyl)-6-benzyloxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(22) and (3aS, 4R, 6S, 11bR, 11cR)-2, 3, 3aα, 4α, 6α, 7, 11bβ, 11cα-octahydro-4-(2′-quinolinyl)-6-benzyloxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-3-carboxylate(23). After boiling under reflux in acetonitrile for 20h. under an argon atmosphere the pmr spectrum of the reaction mixture indicated 70% conversion to a 3:2 mixture of (17) and (18). Flash chromatography eluting with 8:2 v/v ether-petroleum ether afforded the pure isomers in 64% combined yield.

22. The product crystallised from CH_2Cl_2-petroleum ether as colourless plates, m.p. 172°C; $[\alpha]_D$-32.0° (c.0.2, CH_2Cl_2); (Found: C, 74.2; H, 5.2; N, 8.0. $C_{32}H_{27}N_3O_4$ requires C, 74.25, H, 5.2; N, 8.1%); m/z(%) 517(M^+,34), 426(49), 382(98), 271(100), 167(27), 143(55) and 91(62); δ 8.05-7.03(m, 15H, ArH), 5.03(s, 1H, 4-H), 4.84(q, 2H, J 12.3, 45.4 and 12.3Hz, $PhCH_2$), 4.84(d, 1H, J 8.3Hz, 11b-H), 4.69(d, 1H, J 8.0Hz, 3a-H), 3.86-3.80(m, 2x1H, 11c-H and 6-H), 3.06-3.02(m, 2H, 7-CH_2), and 2.88(s, 3H, NMe); ^{1}H NOEDS(%): irradiation of 11b-H caused enhancement of 11c-H (14.45). Irradiation of 3a-H proton caused enhancement of 11c-H (11.06) and 4-H (4.42).

23. The product crystallised from CH_2Cl_2-petroleum ether as tiny colourless prisms, m.p. 167°C; $[\alpha]_D$-2.4°(c.0.3, CH_2Cl_2); (Found: C, 74.15; H, 5.15; N, 8.1%); m/z(%) 517(M^+,52), 426(26), 382(100), 271(43), 167(38), 143(43) and 91(88); δ 8.06-7.1(m, 15H, ArH), 5.22(s, 1H, 11b-H), 5.08(s, 2H, $PhCH_2$), 4.64(d, 1H, J 8.2, 4-H), 3.7-3.67(m, 3x1H, 11c-H, 3a-H and 6-H); 3.2 (dd, 1H, J 6.5 and 10.3Hz, 7-H), 2.99(s, 3H, NMe) and 2.84(d, 1H, J 28.6Hz, 7-H); ^{1}H NOEDS(%): irradiation of 4-H caused enhancement of 3a-H (21.7), irradiation of 11b-H caused enhancement of 11c-H (5.34).

2,3,3aβ,4α,6α7,12bβ,12cβ-Octahydro-4-[(1′R,2′S,5′R)-2′-isopropyl-5′-methylcyclohexyloxycarbonyl]-6-methoxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-4,3]indolizino[8,7-b]-12H-indole-1,3-dione(25a). Methyl (S)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (0.25g, 1.1mmol), menthyl glyoxylate monohydrate (0.25g, 1.1mmol) and NMM (0.12g, 1.1mmol) were mixed in DMF (20ml) and heated at 120°C, for 18h. The pmr spectrum of the reaction mixture showed the presence of two isomers in a ratio of 3.5:1. Work up and column chromatography eluting with 6:4 v/v ether-petroleum ether afforded the major isomer as a pale yellow solid

(0.29g, 51%), which crystallised from ether-petroleum ether as pale yellow needles, m.p. 128-130°C; $[\alpha]_D$ + 104.2°(c.0.06, CH_2Cl_2). Attempts to isolate the minor isomer were unsuccessful. (Found: C, 65.4; H, 6.7; N, 7.55. $C_{38}H_{37}N_3O_6$. H_2O requires C, 65.1; H, 6.7; N, 7.6%); δ 8.25(brs, 1H, NH), 7.44 and 7.33 (2xd, 2x1H, ArH), 7.17 and 7.08(2xt, 2x1H, ArH), 5.46(d, 1H, J 8.6Hz, 12b-H), 4.78(dt, 1H, J 4.3 and 6.7Hz, menthyl-H), 4.20(t, 1H, J 8.1Hz, 3a-H), 4.14(d, 1H, J 2.75Hz, 4-H), 3.87(t, 1H, J 8.55Hz, 12c-H), 3.67(dd, 1H, J 11.4 and 8.45Hz, 6-H), 3.59(s,3H, OMe), 3.13(brs, 2H, 7-CH_2), 2.79(s, 3H, NMe), 2.05 and 1.91(2xm, 2x1H, menthyl-H), 1.68(m, 2H, menthyl-H), 1.52(m, 1H, menthyl-H), 1.0-1.50(m, 4H, menthyl-H), 0.92 and 0.86 (2xd, 2x3H, $CH\underline{Me}_2$), and 0.78(d, 3H, J 6.96Hz, Me); m/z% 535(M^+,46), 534(100), 396(68), 352(76), 266(19), 241(12), 183(12), 155(15), 139(12) and 111(11).

2,3,3aβ,4α,6α,7,12bβ,12cβ-Octahydro-4,6-di(methoxycarbonyl)-2-methyl-1H-pyrrolo[3′,4′-4,3]indolizino[8,7-b]-12H-indole-1,3-dione(25b) and 2,3,3aα,4α,6α,7,12bβ,12cα-octahydro-4,6-di(methoxycarbonyl)-2-methyl-1H-pyrrolo[3′,4′-4,3]indolizino[8,7-b]-12H-indole-1,3-dione(26). After 15h. boiling under reflux in acetonitrile, under an atmosphere of argon the pmr spectrum of the reaction mixture indicated 76% conversion to two products in a 3:1 ratio. Flash chromatography eluting with 9:1 v/v ether-petroleum ether afforded two isomers in 68% combined yield.

25b. The product crystallised from CH_2Cl_2-petroleum ether as pale yellow needles, m.p. 242°C; $[\alpha]_D$-1.1°(c.0.8, CH_2Cl_2); (Found: C,61.3; H,5.3; N,9.95. $C_{21}H_{21}N_3O_6$ requires C,61.3; H,5.1; N,10.2%); m/z(%) 411(M^+,59), 352(100) 266(26), 241(28), 207(27), 103(37) and 84(34); δ 8.24(s,1H,NH), 7.44-7.08(m,4H,ArH), 5.35(d,1H, J 8.5Hz, 12b-H), 4.25(s,1H,4-H), 4.2(m,1H,6-H), 3.81(t,1H, J 8.3Hz, 12c-H), 3.71(s,3H,OMe), 3.68(d,1H, J 8.1Hz, 3a-H), 3.58(s,3H,OMe), 3.14-3.11(m,2H,CH_2) and 2.82(s,3H,NMe); ^{1}H NOEDS(%): irradiation of the 12b-H caused enhancement of the 12c-H (15.1). Irradiation of the 3a-H caused enchancement of 12c-H (13.2) and 4-H (4.4).

26. The product crystallised from CH_2Cl_2-petroleum ether as pale yellow needles, m.p. 142°C; $[\alpha]_D$ + 44.0°(c.0.3, CH_2Cl_2); (Found: C,61.3; H,5.3; N,8.95%); m/z(%) 411(M^+,61), 352(57), 316(56), 205(100), 173(51), 131(92) and 91(86); δ 8.31(s,1H,NH), 7.48-7.09(m,4H,ArH), 4.77(d,1H, J 7.8Hz, 12b-H), 4.5(m,1H,6-H), 4.46(d,1H,J 7Hz,4-H), 3.86(s,3H,OMe), 3.63-3.57(m,2x1H, 12c-H and 3a-H), 3.59(s,3H,OMe), 3.24(m,2H,CH_2) and 2.83(s,3H,NMe); ^{1}H NOEDS(%): irradiation of the 12b-H caused enhancement of 12c-H (4.62). Irradiation of the 4-H caused enhancement of 3a-H (12.4).

2,3,3aβ,4α,6α,7,12bβ,12cβ-Octahydro-4-benzoyl-6-methoxycarbonyl-2-methyl-1H-pyrrolo[3′,4′-4,3]indolizino[8,7-b]-12H-indole-1,3-dione(25c). After 20h. boiling under reflux in acetonitrile under an atmosphere of argon, the pmr spectrum of the reaction mixture indicated 67% conversion to product. Flash chromatography eluting with 6:4 v/v ethyl acetate-petroleum ether, afforded a single *product* (73%) which crystallised from ethyl acetate-petroleum ether as pale yellow plates, m.p. 151°C; $[\alpha]_D$ + 86.7° (c.0.3, CH_2Cl_2); (Found: C,68.2; H,5.0; N,8.95. $C_{26}H_{23}N_3O_5$ requires C,68.25; H,5.05; N,9.2); m/z(%) 457(M^+,24), 439(17), 378(52), 352(100), 207(22), 168(29) and 105(65); δ 8.39(s,1H,NH), 8.1(d,2H, J 7.2Hz,ArH), 7.6-7.04(m,7H,ArH), 5.35(d,1H, J 8.5Hz, 12b-H), 5.29(s,1H,4-H), 4.11(t,1H, J 7.1Hz, 6-H), 3.88(t,1H, J 8.3Hz, 12c-H), 3.62(d,1H,J 6.4Hz,3a-H), 3.18(s,3H,OMe), 3.13(m,1H,CH_2), 3.03(m,1H,CH_2), and 2.84(s,3H,NMe); ^{1}H NOEDS(%): irradiation of the 12b-H caused enhancement of the signal for the 12c-H (12.3). Irradiation of the 4-H caused enhancement of 3a-H (3.9).

Cycloadducts (29a) - (32a) from methyl (S)-thiazolidine-4-carboxylate. Methyl (S)-thiazolidine-4-carboxylate (1.0g, 6.84mmol), methyl glyoxylate monohydrate (0.725g, 6.8mmol) and N-methylmaleimide (0.76g, 6.8mmol) were mixed in DMF (50ml) and heated at 120°C for 12h. The residue was purified by flash chromatography eluting with 3:2 v/v ether-petroleum ether to afford the products (29a)-(32a) together with

(33).

29a. The product (0.829g, 37%) crystallised ether-petroleum ether as colourless needles, m.p. 137° (Found: C, 47.75 ; H, 4.95; N, 8.7. $C_{13}H_{16}N_2O_6S$ requires C, 47.55, H, 4.9; N, 8.55%); δ 4.33(d, 1H, J 8.2Hz, H_C), 4.12 and 3.91(2xd, 2x1H, J 7.1Hz, H_D), 3.74(2xs, 1xt, 7H, 2xOMe and H_B), 3.52(d, 1H, J 8.9Hz, H_A), 3.28(d, 1H, J 11.2Hz, H_E) and 3.07(d and s, 4H, NMe and H_E); ^{1}H NOEDS (%): irradiation of H_B caused enhancement of the signals for H_A (13.1) and H_C (11.7); m/z(%) 328(M^+, 1), 269(100), 209(19), 138(16), 84(12) and 45(35).

30a. The product (0.41g, 18.4%) crystallised from ether-petroleum ether as colourless prisms m.p. 168°C (Found: C, 47.6; H, 4.95; N, 8.65%); δ 4.6(d, 1H, J 10.2Hz, H_D), 4.31(s, 1H, H_C); 4.14(d, 1H, J 10.3Hz, H_D), 3.94(d, 1H, J 11.2Hz, H_B), 3.8(m and 2xs, 8H, H_A, H_E and 2xOMe), 3.01(s, 3H, NMe) and 2.93(d, 1H, J 10.6Hz, H_E); ^{1}H NOEDS (%): irradiation of H_B caused enhancement of the signals for H_A (8.1) and H_C (2.3); m/z(%) 328(M^+,4), 269(100), 209(36), 138(27), and 45(17).

31a. The *product* (0.132g, 7%) crystallised from methylene chlorid-petroleum ether as colourless prisms, m.p. 127°C. Accurate mass 270.1624. $C_{11}H_{14}N_2O_4S$ requires 270.1624. δ 4.25 and 3.95 (2xd, 2x1H, J 10Hz, H_D), 3.82 (s, 3H, OMe), 3.53 (t and d, 2H, H_B and H_C), 3.46 (d, 1H, J 11 Hz, H_E), 3.05 (dd, 1H, J 4.7 and 5 Hz, H_C), 2.98 (d, 1H, H_E) and 2.96 (s, 3H, NMe); m/z (%) 270 (M^+, 6), 211 (100), 167 (21), 126 (49) and 80 (51).

32a. The *product* (62mg, 3.5%) crystallised from methylene chloride-petroleum ether as colourless needles, m.p. 102°C. Accurate mass 270.1624. δ 4.23 and 4.12 (2xd, 2x1H, J 10.6 Hz, H_D), 3.81 (s, 3H, OMe), 3.73 (d, 1H, J 9.7 Hz, H_A), 3.56 (2xd, 2H, H_E and H_C), 3.37 (t, 1H, J 7.5 and 8 Hz, H_B), 3.0 (s, 3H, NMe), 2.98 (dd, 1H, J 5.5 and 6 Hz, H_C) and 2.8 (d, 1H, J 11 Hz, H_E); m/z (%). 270 (3), 211 (100), 126 (83), 80 (37) and 59 (25).

33. Major isomer (0.189g, 13.5%) obtained as a colourless oil, δ 5.18 (s, 1H, 2-H), 4.47 (t, 1H, J 5.6 and 5.8Hz, 4-H); 3.82 (s, 1H, NH), 3.77 and 3.74 (2xs, 2x3H, 2xOMe), and 3.27 and 3.1 (2xdd, 2x1H, 5-H); m/z (%) 205 (M^+, 2), 146 (100), 86 (69) and 59 (24). Minor isomer (0.156g, 11%) obtained as a colourless oil. δ 4.98 (s, 1H, 2-H), 2.83 (dd and 2xs, 7H, 4-H and 2xOMe), 3.32 and 2.82 (2xdd, 2x1H, 5-H); m/z (%) 205 (M^+, 2), 146 (100), 86(51) and 59(37).

Cycloadducts (29b)-(31b) from methyl (S)-thiazolidine-4-carboxylate. Methyl (S)-thiazolidine-4-carboxylate (1.0g, 6.84mmol), phenylglyoxal monohydrate (1.04g, 6.84mmol) and NMM (0.76g, 6.84mmol) were dissolved in DMF (50ml) and heated at 120°C for 16h. Work up as above followed by flash chromatography eluting with ether afforded the *products* (29b)-(31b).

29b. The product (1.07g, 42%) crystallised from methylene chloride-petroleum ether as colourless microprisms, m.p. 136°C (Found: C, 57.45; H, 4.7; N, 7.4. $C_{18}H_{18}N_2O_5S$ requires C, 57.75; H, 4.8; N, 7.5%); δ 8.01(d, 2H, ArH), 7.67-7.45(m, 3H, ArH), 5.43(d, 1H, J 7.9Hz, H_C), 4.21(d, 1H, J 5.7Hz, H_D), 4.02(t, 1H, J 8.1Hz, J 6.9Hz, H_B), 3.87(s, 3H, OMe), 3.86(d, 1H, J 4.2Hz, H_D), 3.51(d, 1H, J 8.3Hz, H_A), 3.38 and 3.11(2xd, 2x1H, J 7.2Hz, H_E) and 2.98(s, 3H, NMe); ^{1}H NOEDS (%): irradiation of H_C caused enhancement of the signal for H_B (8.2); irradiation of H_B caused enhancement of the signals for H_c (8.0) and H_A (7.2); m/z(%) 374(M^+,10), 315(18), 269(100), 241(16), 105(38), 77(19) and 45(13).

30b. The product (0.39g, 15.4%) crystallised from methylene chloride-petroleum ether as colourless plates m.p. 169°C (Found: C, 57.45; H, 4.6; N, 7.45%); δ 8.03(d, 2H, ArH), 7.67-7.45(m, 3H, ArH), 5.10(s, 1H, H_C), 4.49(d, 1H, J 9.4Hz, H_D), 4.18(d, 1H, J 8.8Hz, H_A), 4.06(d, 1H, J 10.6Hz, H_D), 3.94(d, 1H, J 7.7Hz, H_B), 3.69(s, 3H, OMe), 3.62 and 3.31 (2xd, 2x1H, H_E), and 3.01(s, 3H, NMe); ^{1}H NOEDS (%): irradiation of H_B effected enhancement of the signals for H_A (14.5) and H_C (3.6); m/z(%) 374 (M^+,3), 315(11), 269(100), 241(14), 105(69), 77(42) and 45(14).

31b. The product (0.388g, 15.3%) crystallised from methylene chloride-petroleum ether as colourless plates,

m.p. 205°C (Found: C, 57.65; H, 4.65; N, 7.5%); δ 8.06(d, 2H, ArH), 7.73(m, 3H, ArH), 5.33(s, 1H, H_C), 4.09 (AB, 2H, J 10.4Hz, H_D), 3.97(d, 2H, H_E,H_B), 3.76(s, 3H, OMe), 3.75(d, 1H, J 6.9Hz, H_A), 3.05(s, 3H, NMe) and 3.01(d, 1H, J 9.5Hz, H_E); ^{1}H NOEDS(%): irradiation of H_B effected enhancement of the signal for H_A (7.3) but no enhancement of the signal for H_C was observed.

1,2,3,3aβ,4β,5,6,11,11a,11bβ,-Decahydro-2-methyl-4-(2′-methoxyphenyl)-11a-methoxycarbonyl-1H-pyrrolo[3′,4′-3,4] pyrrolo [2,1-b] isoquinoline-1,3-dione (38) and 1,2,3,3aα,4β,5,6,11,11a,11bα-decahydro-2-methyl 4-(2′-methyoxyphenyl)-11a-methoxycarbonyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-b]isoquinoline-1,3-dione (39). Methyl (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.16g, 8.4mmol), aldehyde (0.11g, 8.4mmol) and NMM (0.089g, 8.4mmol) were mixed in toluene (15ml) and heated under reflux for 18h. The residue was purified by flash chromatography eluting with 1:1 v/v ether-petroleum ether to afford (38) (0.13g, 37%) and (39) (0.15g, 43%) as a colourless crystalline solids.

38. Colourless prisms from benzene m.p. 98-100°C (Found: C, 68.7; H, 5.7; N, 6.7. $C_{24}H_{24}N_2O_5$ requires: C, 68.55, H, 5.7; N, 6.65%); δ 7.29-6.85(m, 8H, ArH), 5.13(d, 1H, J 9.46Hz, 4-H), 3.98(d, 1H, J 15.5Hz, 5_β-H), 3.93(s, 3H, OMe), 3.82(d, 1H, J 15.4Hz, 5_α-H), 3.72(t, 1H, J 8.05Hz, 3a-H), 3.64(s, 3H, CO_2Me), 3.60(d, 1H, J 15.9Hz, 10-H), 3.52(2xm, 2x1H, 10-H and 11bH) and 2.76(s, 3H, NMe); m/z(%) 420(M^+,56), 361(100), 309(4), 253(8), 250(4) and 143(4).

39. Colourless prisms from ether-petroleum ether m.p. 208-210°C. (Found: C, 68.3; H, 5.7; N, 6.7%), δ (C_6D_6) 7.41(d, 1H, J 7.57Hz, ArH), 7.12-6.95(m, 4H, ArH), 6.83(t, 1H, ArH), 6.61 and 6.48 (2xd, 2x1H, ArH), 5.49(brs, 1H, 4-H), 3.85(d, 1H, J 15.27Hz, 5_β-H), 3.67(d, 1H, J 8.15Hz, 3a-H) 3.60(d, 1H, J 8Hz, 11b-H, 3.45(brs, 3H, OMe), 2.99(s, 3H, CO_2Me), 2.92(d, 1H, J 14.74Hz, 5α-H, 2.86(brs, 2H, 10-H) and 2.69 (s, 3H, NMe); m/z(%) 420(M^+, 1), 361(100), 253(6), 239(5), 143(5) and 131(6).

Single crystal X-ray diffraction analysis of 15a - All crystallographic measurements were carried out at 200 K on a Stoe STADI4 diffractometer using graphite monochromated Copper K_α X-radiation (λ = 1.54184 Å). Data were collected in the range 4.0° < 2θ < 120.0° using ω-θ scans and a learnt profile[12] method. No significant variation was observed in the intensities of three standard reflections. The structure was solved by direct methods using SHELXS.[13] The structure was refined by full-matrix least-squares (based on F^2) using the SHELXL93[14] program system which uses all data in refinement. The weighting scheme was $w = [\sigma^2(F_o^2) + (0.0453P)^2 + 0.6063P]^{-1}$ where $P=(F_o^2 + 2F_c^2)/3$.

All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions (C-H = 1.00, 0.99, 0.98 and 0.95Å, for primary, secondary, tertiary and aromatic hydrogens respectively) and given fixed isotropic thermal parameters of $n(U_{eq})$ of the parent carbon atom, where n is 1.5 for methyl hydrogen atoms and 1.2 for all others) . Refinement included an isotropic extinction parameter x, so that $F_c'' = k F_c[1 + 0.001 * x * F_c^2 * \lambda^3]^{-¼}$ where k is the overall scale factor. The absolute structure was based on the known configuration of the (-)-menthyl substituent. The parameters wR_2 and R_1 are defined as $wR_2 = (\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[wF_o^4])^{½}$ and $R_1 = \Sigma \mid |F_o| - |F_c| \mid / |F_o|$. The latter is given for comparison with refinements based on F and uses reflections with $F_o > 4.0\ \sigma(F_o)$.

Crystal data - $C_{28}H_{36}N_2O_6$, 0.4 x 0.2 x 0.2 mm, M = 496.59, monoclinic, space group $P2_1$, a = 10.5933(5), b = 9.5673(7), c = 13.6124(9) Å, β = 111.256(4)°, U = 1285.75(14) Å^3, Z = 2, D_x = 1.283 Mg m^{-3}, μ = 0.733 mm^{-1}, F(000) = 532.
Data collection - Each scan was divided into 30 steps with scan width and step sizes calculated from a learnt profile, 4.0 < 2θ < 120.0°, 2218 Data collected 2010 of which were unique, R_{sig} = 0.0124. There were 1967 reflections with $F_o > 4.0\ \sigma(F_o)$.
Structure refinement - Number of parameters = 330, isotropic extinction parameter x = 0.012(1), goodness of fit s = 1.117, wR_2 = 0.0940, R_1 = 0.0346.
Non-hydrogen atomic co-ordinates are given in Table A and bond lengths are in Table B.
Supplementary data, which includes hydrogen co-ordinates and all thermal parameters together with complete bond lengths and angles, has been deposited at the Cambridge Crystallographic Data Centre and is available on request.

References

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